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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,181	VARNER ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/15/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/15/08 has been entered.

Applicant elected previously the following species: (a) endothelial cell as a species of a cell; and (b) cancer as a species of a pathological condition.

Claims 25-40 are pending in the present application, and they are examined on the merits herein with the aforementioned elected species.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

With respect to the elected species of endothelial cells, claims 25-28 and 32-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

1. A method for reducing angiogenesis in a tumor tissue, comprising:

a) providing:

i) a tumor tissue comprising endothelial cells; and

ii) an isolated nucleotide sequence encoding a protein comprising a protein kinase A (PKA) catalytic subunit; and

b) expressing said nucleotide sequence in said endothelial cells to produce a treated tumor tissue, such that angiogenesis by said endothelial cells in said treated tumor tissue is reduced;

2. A method for increasing apoptosis, comprising:

a) providing:

i) a tumor tissue comprising endothelial cells; and

ii) an isolated nucleotide sequence encoding a protein comprising a protein kinase A (PKA) catalytic subunit; and

b) expressing said nucleotide sequence in said endothelial cells such that apoptosis in said endothelial cells is increased;

does not reasonably provide enablement for a method for reducing angiogenesis in any other tissues or a method for increasing apoptosis in any other tissue comprising endothelial cells, let alone for other cell types as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte*

Forman, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)). ***This is a new ground of rejection.***

The instant specification is not enabled for a method of reducing angiogenesis in a tissue or a method for increasing apoptosis as broadly claimed for the following reasons.

1. The breadth of the claims

Claims 25-28 and 32 are directed to a method for reducing angiogenesis in any tissue comprising endothelial cells, not necessarily limited to a tumor tissue comprising endothelial cells, by expressing a nucleotide sequence encoding a protein comprising a protein kinase A (PKA) catalytic subunit in the endothelial cells.

Claims 33-37 are directed to a method for increasing apoptosis of any cells (with endothelial cells as the elected species) in any tissue, not necessarily limited to a tumor tissue comprising tumor associated endothelial cells and/or tumor cells, by expressing in the cells a nucleotide sequence encoding a protein comprising a protein kinase A (PKA) catalytic subunit.

2. The state of the prior art and the unpredictability of the prior art

At the effective filing date of the present application (6/25/02), little was known about reducing angiogenesis in any tissue comprising endothelial cells by expressing in said endothelial cells an isolated nucleotide sequence encoding a protein comprising a PKA catalytic subunit or about increasing apoptosis in any tissue comprising any cells, including endothelial cells (elected species) by simply expressing in said cells an isolated nucleotide sequence encoding a protein comprising a PKA catalytic subunit as

evidenced at least by the teachings of Kim et al. (J. Biol. Chem. 275:33920-33928, 2000: IDS), Kim et al. (Am. J. Pathol. 156:1345-1362, 2000; IDS), Stupack et al. (J. Cell Biology 155:459-470, 2001), Kim et al. (Biochem. Biophys. Res. Comm. 232:469-473, 1997), Srivastava et al. (Mol. Cell. Biol. 18:3509-3517, 1998) and Amano et al. (Jpn. J. Pharmacol. 87:181-188, 2001; IDS). Although Kim et al (J. Biol. Chem. 275:33920-33928, 2000) already teach that **agents that activate intracellular protein kinase A (PKA) such as forskolin, dibutyryl cAMP or α5β1 antagonists suppress endothelial cell migration on vitronectin *in vitro* or angiogenesis *in vivo*, while inhibitors of PKA including H89 which is a selective inhibitor of PKA, reverse the anti-migratory or anti-angiogenic effects mediated by α5β1 antagonists** (see at least the abstract; page 33924, col. 2, last paragraph continues to first paragraph of col. 1 on page 33925; Figures 4-7); **Amano et al also teach that adenylate cyclase/protein kinase A signaling pathway enhances angiogenesis through induction of vascular endothelial growth factor in a rat sponge implantation model in which the sponge granulation tissues constituted mainly of collagen fibers and VEGF-positive fibroblast-like cells** (see at least the abstract; page 183, col. 1, last sentence continues to first paragraph of col. 2; page 184, col. 2, first paragraph). However, Kim et al. (Am. J. Pathol. 156:1345-1362, 2000) already taught **enhanced expression of fibronectin and its receptor integrin α5β1 on at least human colon carcinoma and breast carcinoma associated blood vessels while blood vessels in normal tissues expressed little, if any, fibronectin and negative for integrin α5β1; and that integrin α5β1 is required for human tumor**

angiogenesis (see at least the sections titled "Enhanced expression of Fibronectin and its receptor integrin $\alpha5\beta1$ on tumor-associated blood vessels"; and "Integrin $\alpha5\beta1$ is required for human tumor angiogenesis"). Additionally, Kim et al. (Am. J. Pathol. 156:1345-1362, 2000) further taught that **antibody, peptide and novel nonpeptide antagonists of $\alpha5\beta1$ blocked or inhibited tumor angiogenesis, causing regression of human tumors in animal models, but these $\alpha5\beta1$ antagonists had little effect on angiogenesis induced by vascular endothelial growth factor (VEGF) or endothelial migration on non-fibronectin extracellular matrix proteins, including collagen** (see at least the abstract and page 1352, col. 2, last paragraph continues to first paragraph of col. 1 on page 1355). Furthermore, Stupack et al also taught that **cells adherent within a three-dimensional exracellular matrix undergo apoptosis due to expression of unligated integrins; and that selective blockade of a single integrin such as $\alpha v\beta3$, $\alpha5\beta1$ and other integrins have been associated with apoptosis** (see at least the abstract and page 459, col. 2, first full paragraph).

3. The amount of direction or guidance provided

Apart from a tumor tissue, the instant specification fails to provide sufficient guidance for a skilled artisan on how to reduce angiogenesis in any other tissues comprising endothelial cells by simply expressing an isolated nucleotide sequence encoding a protein comprising a PKA catalytic subunit, particularly in light of the teachings of Amano et al that disclose that adenylate cyclase/protein kinase A signaling pathway **enhances angiogenesis rather than reducing angiogenesis** through induction of vascular endothelial growth factor *in vivo*. Moreover, Kim et al. (Am. J.

Pathol. 156:1345-1362, 2000) also taught **α5β1 antagonists (e.g., antibody, peptide, novel nonpeptide antagonists and please note that exogenous expression vector encoding PKA subunit is a functional equivalent of an α5β1 antagonist) had little effect on endothelial migration on non-fibronectin extracellular matrix proteins, including collagen**. Furthermore, the instant specification also fails to provide sufficient guidance for a skilled artisan on how to increase apoptosis in any tissue comprising endothelial cells by simply expressing in said cells a nucleotide sequence encoding a protein comprising a PKA catalytic subunit, let alone for a tissue comprising cells such as fibroblasts, smooth muscle cells, neurons, synoviocytes and others, particularly at least in light of the teachings of Amano et al. and , Kim et al. (Am. J. Pathol. 156:1345-1362, 2000). Since the prior art do not provide such guidance, it is incumbent upon the present application to do so. Moreover, the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the physiological art with respect to the angiogenesis and/or apoptosis processes in a tissue comprising cells, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 25-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (J. Biol. Chem. 275:33920-33928, 2000: IDS) in view of Kim et al. (Am. J. Pathol. 156:1345-1362, 2000; IDS), Stupack et al. (J. Cell Biology 155:459-470, 2001), Kim et al. (Biochem. Biophys. Res. Comm. 232:469-473, 1997), Srivastava et al. (Mol. Cell. Biol. 18:3509-3517, 1998) and Mixson, A. J. (US 6,080,728). ***This is a new ground of rejection.***

Within the scope of enablement, Kim et al (J. Biol. Chem. 275:33920-33928, 2000) already teach that agents that activate intracellular protein kinase A (PKA) such

as forskolin, dibutyryl cAMP or α5β1 antagonists suppress endothelial cell migration on vitronectin *in vitro* or angiogenesis *in vivo*, while inhibitors of PKA including H89 which is a selective inhibitor of PKA, reverse the anti-migratory or anti-angiogenic effects mediated by α5β1 antagonists (see at least the abstract; page 33924, col. 2, last paragraph continues to first paragraph of col. 1 on page 33925; Figures 4-7). Kim et al also teach that ligation of α5β1 by fibronectin suppresses protein kinase A activation and permits the association of αvβ3 with the actin cytoskeleton as well as cellular migration, while inhibiting α5β1 ligation with antagonists of α5β1 or the fibronectin cell-binding domain promotes the dissociation of the catalytic subunit from the regulatory subunit of protein kinase A, thereby activating the kinase and inhibiting αvβ3-mediated focal contact and stress fiber formation, as well as migration (page 33926, col. 2, last paragraph and Figure 8). This is a type of control or means that α5β1 exerts over αvβ3 *in vivo* at the cellular level through a precise mechanism to maintain orderly outgrowth of blood vessels since *in vivo*, fibronectin and integrins α5β1 and αvβ3 are simultaneously expressed on the endothelial cells of tumor blood vessels and of tissues exposed to angiogenic growth factors; and while integrin α5β1 is largely selective for fibronectin which is a component of the provisional matrix expressed by endothelial cells during wound healing or tumor angiogenesis, and in contrast integrin αvβ3 is a promiscuous integrin with the potential to mediate migration on a host of extracellular matrix proteins with arginine-glycine-aspartic acid moieties (page 33926, col. 2, last paragraph continues to first paragraph of col. 1 on page 33927). Kim et al further stated "These studies also suggest the potential use of PKA agonists in the treatment of

angiogenic diseases, including cancer and arthritis" (page 33927, col. 2, last paragraph continues to first two lines in col. 1 of page 33928).

Kim et al (J. Biol. Chem. 275:33920-33928, 2000) do not teach specifically the use of an isolated nucleotide sequence encoding a protein comprising a protein kinase A (PKA) catalytic subunit as the agent or the PKA agonist in a method for reducing angiogenesis or for increasing apoptosis in a tissue comprising endothelial cells (elected species), and/or wherein the tissue is in a subject having cancer (elected species) as a pathological condition associated with angiogenesis.

At the effective filing date of the present application (6/25/02), Kim et al. (Am. J. Pathol. 156:1345-1362, 2000) already taught **enhanced expression of fibronectin and its receptor integrin α5β1 on at least human colon carcinoma and breast carcinoma associated blood vessels while blood vessels in normal tissues expressed little, if any, fibronectin and negative for integrin α5β1; and that integrin α5β1 is required for human tumor angiogenesis** (see at least the sections titled "Enhanced expression of Fibronectin and its receptor integrin α5β1 on tumor-associated blood vessels"; and "Integrin α5β1 is required for human tumor angiogenesis"). Kim et al. (Am. J. Pathol. 156:1345-1362, 2000) further taught that **antibody, peptide and novel nonpeptide antagonists of α5β1 blocked or inhibited tumor angiogenesis, causing regression of human tumors in animal models, but these α5β1 antagonists had little effect on angiogenesis induced by vascular endothelial growth factor (VEGF) or endothelial migration on non-fibronectin**

extracellular matrix proteins, including collagen (see at least the abstract and page 1352, col. 2, last paragraph continues to first paragraph of col. 1 on page 1355).

Stupack et al also taught that **cells adherent within a three-dimensional exracellular matrix undergo apoptosis due to expression of unligated integrins; and that selective blockade of a single integrin such as αvβ3, α5β1 and other integrins have been associated with apoptosis** (see at least the abstract and page 459, col. 2, first full paragraph).

Additionally, Kim et al (Biochem. Biophys. Res. Comm. 232:469-473, 1997) already taught at least that overexpression of a protein kinase A catalytic subunit meditated by a recombinant retroviral vector in SK-N-SH human neuroblastoma cells resulted in a 3-fold increased PKA activity, increased type II protein kinase A activity and cellular growth inhibition (see at least the abstract; and Results and Discussion on pages 470-472).

Moreover, Srivastava et al taught that activation of cAMP-dependent protein kinase A by Paclitaxel, forskolin or okadaic acid induced Bcl2 hyperphosphorylation and apoptosis in cancer cells which were blocked by the PKA inhibitor Rp diastereomers of cAMP (see at least the abstract; page 3511, col. 2, the section entitled "cAMP-dependent protein kinase is involved in Bcl2 phosphorylation", page 3510, col. 2, the section entitled "Nuclear morphology").

Furthermore, at the effective filing date of the present application Mixson also taught successfully at least a method for inhibiting tumor growth in a subject bearing a tumor comprising injection of DNA encoding at least one anti-angiogenic protein or

peptide specifically targeting the tumor and/or tumor vasculature (see at least Summary of the Invention; and issued claims). Mixson disclosed that the method is applicable to different types of tumors, including primary tumors and their metastases or malignant tumor cells, and all of the tumors are very dependent on blood supply to sustain their growth (col. 10, lines 15-19; col. 4, lines 47-54 and example 1).

Accordingly, it would have been obvious for an ordinary skilled artisan at the time of invention was made to modify the teachings of Kim et al (J. Biol. Chem. 275:33920-33928, 2000) by at least expressing a nucleotide sequence encoding a protein comprising a protein kinase A catalytic subunit in a tumor tissue comprising tumor associated endothelial cells, for example in a tumor vasculature, to induce anti-angiogenic effects and/or apoptotic effects to inhibit tumor growth in light of the teachings of Kim et al. (Am. J. Pathol. 156:1345-1362, 2000), Stupack et al., Kim et al. (Biochem. Biophys. Res. Comm. 232:469-473, 1997), Srivastava et al., and Mixson, A. J.

An ordinary skilled artisan would have been motivated to carry out the above modification because expression a nucleotide encoding a protein kinase A catalytic subunit is a means for the activation of intracellular protein kinase A that has been demonstrated to be involved in the suppression of endothelial cell migration on vitronectin *in vitro* and inhibiting angiogenesis *in vivo*, which alters the ligation state of integrin $\alpha 5\beta 1$ on endothelial cells, coupled with the knowledge of specific enhanced expression of fibronectin and its receptor integrin $\alpha 5\beta 1$ on tumor associated blood vessels and that integrin $\alpha 5\beta 1$ is required for human tumor angiogenesis as well as

selective blockade of a single integrin such as $\alpha v\beta 3$, $\alpha 5\beta 1$ and other integrins have been associated with apoptosis. Furthermore, activation or overexpression of intracellular protein kinase A has also been shown to inhibit human neuroblastoma cell growth *in vitro*, as well as the induction of Bcl2 hyperphosphorylation and apoptosis in cancer cells *in vitro*.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Kim et al (J. Biol. Chem. 275:33920-33928, 2000), Kim et al. (Am. J. Pathol. 156:1345-1362, 2000), Stupack et al., Kim et al. (Biochem. Biophys. Res. Comm. 232:469-473, 1997), Srivastava et al. and Mixson, A. J.; coupled with a high level of skill of an ordinary artisan in the relevant art.

Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related in part with respect to the above new ground of rejection in the Amendment filed on 12/15/08 (pages 5-12) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

1. Applicants argue that the prior art Amano et al which was cited by Applicants and not used in the rejection, teaches away from claims 25-32 because the reference teaches specifically that PKA increases angiogenesis that is diametrically opposite from independent claim 25. Applicants also argue that the Amano et al reference was published in 2001 which is after the publication date in 2000 of the

primary reference of Kim et al, and therefore Amano et al's objective assessment of the state of the prior art as a whole was that PKA increased rather than decreased angiogenesis. Therefore, one of skill in the art would proceed in a direction that is diametrically opposite from the direction undertaken by the inventors which is contrary to the accepted wisdom, and this is also a strong evidence of unobviousness. Applicants further argue that there was also uncertainty about whether the primary Kim et al reference's anti-angiogneic effects of forskokin and cAMP were the result of activation of Epac, of PKA or other pathways that were referred by statements such as "that activation of Rap1 by forskolin and cAmP occurs independently of protein kinase A" and "that not all cAMP-induced effects are mediated by either PKA or cyclic-nucleotide-gated channels, the only previously known cAMP-target proteins. Several reports have suggested the existence of such pathways..." made by the De Rooij et al reference which was also cited by Applicants and not used in the rejection. Once again, Applicants argue that Kim et al (1997) relates to a different cell type (neuroblastoma cells vs endothelial cells) and different phenomenon (growth versus angiogenesis) and that there is no factual evidence that validates the propriety of extrapolating between both the different cells and different phenomenon; the Mixson reference relates to a different phenomenon (tumor growth versus angiogenesis) and Srivastava et al reference refers to a different phenomenon (apoptosis versus angiogenesis).

Firstly, there is no teaching away whatsoever by the Amano et al reference and that this reference does not represent the full picture of the state of angiogenesis at the effective filing date of the present application (6/25/02). **At best, Amano et al teach**

simply that adenylate cyclase/protein kinase A signaling pathway enhances angiogenesis through induction of vascular endothelial growth factor in a rat sponge implantation model in which the sponge granulation tissues constituted mainly of collagen fibers and VEGF-positive fibroblast-like cells (see at least the abstract; page 183, col. 1, last sentence continues to first paragraph of col. 2; page 184, col. 2, first paragraph). The teachings of Amano et al do not contradict to the findings of the primary Kim et al (J. Biol. Chem. 275:33920-33928, 2000) reference that discloses agents that activate intracellular protein kinase A (PKA) such as forskolin, dibutyryl cAMP or $\alpha5\beta1$ antagonists suppress endothelial cell migration on vitronectin *in vitro* or angiogenesis *in vivo*, while **inhibitors of PKA including H89 which is a selective inhibitor of PKA, reverse the anti-migratory or anti-angiogenic effects mediated by $\alpha5\beta1$ antagonists;** and ligation of $\alpha5\beta1$ by fibronectin suppresses protein kinase A activation and permits the association of $\alpha v\beta3$ with the actin cystoskeleton as well as cellular migration, while **inhibiting $\alpha5\beta1$ ligation with antagonists of $\alpha5\beta1$ or the fibronectin cell-binding domain promotes the dissociation of the catalytic subunit from the regulatory subunit of protein kinase A, thereby activating the kinase and inhibiting $\alpha v\beta3$-mediated focal contact and stress fiber formation, as well as migration**; or the findings of Kim et al. (Am. J. Pathol. 156:1345-1362, 2000) that disclose **enhanced expression of fibronectin and its receptor integrin $\alpha5\beta1$ on at least human colon carcinoma and breast carcinoma associated blood vessels while blood vessels in normal tissues expressed little, if any, fibronectin and negative for integrin $\alpha5\beta1$; and that integrin $\alpha5\beta1$ is required for human tumor**

angiogenesis and **antibody, peptide and novel nonpeptide antagonists of α5β1 blocked or inhibited tumor angiogenesis, causing regression of human tumors in animal models, but these α5β1 antagonists had little effect on angiogenesis induced by vascular endothelial growth factor (VEGF) or endothelial migration on non-fibronectin extracellular matrix proteins, including collagen**. Furthermore, Stupack et al also taught that **cells adherent within a three-dimensional exracellular matrix undergo apoptosis due to expression of unligated integrins; and that selective blockade of a single integrin such as αvβ3, α5β1 and other integrins have been associated with apoptosis.** It is also apparent that **the suppression of angiogenesis in vivo and an increased in apoptosis of in cancer or tumor-associated endothelial cells are related and regulated by the ligation state of Integrin α5β1 with its substrate fibronectin and protein kinase A activity**.

Secondly, once again It should be noted that **the conclusions of the study of Kim et al (J. Biol. Chem. 275:33920-33928, 2000) were also based on results obtained from protein kinase inhibitor studies, including the use of H89 which is a specific and selective inhibitor of protein kinase A** (see the abstract and at least sections entitled "Regulation of Integrin cross-talk by protein kinase A" and "Integrin alpa5beta1 and protein kinase A regulation of alphavbeta3-mediated angiogensis in vivo"). Kim et al taught specifically that **inhibitors of PKA reverse the anti-migratory or anti-angiogenic effects** (see at least the abstract; page 33924, col. 2, last paragraph continues to first paragraph of col. 1 on page 33925; Figures 4-7). Kim et al further stated "These studies also suggest **the potential use of PKA agonists in the**

treatment of angiogenic diseases, including cancer and arthritis" (page 33927, col. 2, last paragraph continues to first two lines in col. 1 of page 33928). Therefore, an ordinary skilled artisan would conclude clearly **that the suppression of angiogenesis *in vivo* is mediated by PKA, and not by other protein kinases or by other pathways suggested by Applicants**.

Thirdly, to further support the combined teachings of Kim et al. (J. Biol. Chem. 275:33920-33928, 2000), Kim et al. (Am. J. Pathol. 156:1345-1362, 2000) and Stupack et al. (J. Cell Biology 155:459-470, 2001), at the effective filing date of the present application Kim et al. (Biochem. Biophys. Res. Comm. 232:469-473, 1997) already showed that **overexpression of a protein kinase A catalytic subunit meditated by a recombinant retroviral vector in SK-N-SH human neuroblastoma cells resulted in a 3-fold increased PKA activity, increased type II protein kinase A activity and cellular growth inhibition** and that the concept of **activation of cAMP-dependent protein kinase A by Paclitaxel, forskolin or okadaic acid induced Bcl2 hyperphosphorylation and apoptosis in cancer cells** was also taught by Srivastava et al. The teachings of Mixson, A. J. simply indicated the state of gene therapy art using vectors encoding anti-angiogenic peptides/proteins to treat or inhibit growth of cancers or tumors (please note that growth of a cancer depends on the growth of cancer-associated endothelial cells or angiogenesis).

2. With respect to claims 33-40, once again Applicants reincorporated prior arguments and Dr. Varner's prior Declaration, that argue basically that one of skill in the

art would not have combined the references to arrive at the claims because the primary Klm et al. (2000) reference relates to different phenomena (angiogenesis and cell migration versus apoptosis), Kim et al (1997) relates to a different phenomenon (growth versus apoptosis); Mixon relates to a different phenomenon (tumor growth versus apoptosis) and Srivastava et al's effects on apoptosis could have occurred via PKA-independent pathways and were known to exist at the time of the invention, including via Epac and others. Moreover, Srivastava et al's PKA activators and PKA inhibitors was to reduce apoptosis and to increase apoptosis, respectively, this does not necessarily provide a reasonable expectation of success that using a different methodology such as "expressing" PKA will increase apoptosis. In the absence of objective evidence, a *prima facie* case of obviousness is not established and therefore claims 33-40 are non-obvious.

Firstly, please refer to the teachings of Kim et al (J. Biol. Chem. 275:33920-33928, 2000), Kim et al. (Am. J. Pathol. 156:1345-1362, 2000) and Stupack et al. as discussed above. It is abundantly clear that **the suppression of angiogenesis in vivo and an increased in apoptosis of in cancer or tumor-associated endothelial cells are related and regulated by the ligation state of Integrin $\alpha 5\beta 1$ with its substrate fibronectin and protein kinase A activity**. Once again, please note that growth of a cancer in vivo depends on the growth of cancer-associated endothelial cells or angiogenesis.

Secondly, please note that independent claim 33 encompass **any tissue comprising any cells, including but not necessarily limited to a tumor tissue**

comprising tumor cells and/or tumor associated endothelial cells. Therefore, the teachings of both Kim et al (1997) and Srivastava et al are relevant and related. **Moreover, Srivastava et al also concluded clearly that protein kinase A is involved in the induction of Bcl2 hyperphosphorylation and induction of apoptosis in a peer-reviewed article (see at least the abstract).** To further support the conclusion of Srivastava et al, at the effective filing date of the present application Weissinger et al. (Molecular and Cellular Biology 17:3229-3241, 1997) also taught that **PKA activation induced apoptosis in v-abl-transformed cells and that cAMP agonists might become useful for the treatment of malignancies where abl oncogenes are involved, such as chronic myeloid leukemia** (see at least the abstract).

Thirdly, please also note that none of the above cited references has to disclose and example showing that expressing PKA will increase apoptosis; otherwise such a reference would not be used for a rejection under 35 U.S.C. 103(a).

Finally, an ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Kim et al (J. Biol. Chem. 275:33920-33928, 2000), Kim et al. (Am. J. Pathol. 156:1345-1362, 2000), Stupack et al., Kim et al. (Biochem. Biophys. Res. Comm. 232:469-473, 1997), Srivastava et al. and Mixson, A. J as set forth above, particularly Mixson taught successfully and clearly a method for inhibiting tumor growth in a subject bearing a tumor comprising injection and **expressing any DNA encoding at least one anti-angiogenic protein or peptide specifically targeting the tumor and/or tumor vasculature (made up of endothelial cells); and**

all of the tumors are very dependent on blood supply (requiring angiogenesis) to sustain their growth (col. 10, lines 15-19; col. 4, lines 47-54 and example 1).

Conclusions

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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